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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/544,896	08/08/2005	Masahiro Aoki	016912-0212	6474

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EXAMINER	
BETTON, TIMOTHY E	

ART UNIT	PAPER NUMBER
1617	

MAIL DATE	DELIVERY MODE
04/20/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/544,896	AOKI ET AL.	
	Examiner	Art Unit	
	TIMOTHY E. BETTON	1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12/23/2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-24* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-24* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *See Continuation Sheet*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Continuation of Attachment(s) 3). Information Disclosure Statement(s) (PTO/SB/08), Paper No(s)/Mail Date :1 sheet, 12/7/2005; 1 sheet, 8/8/2005

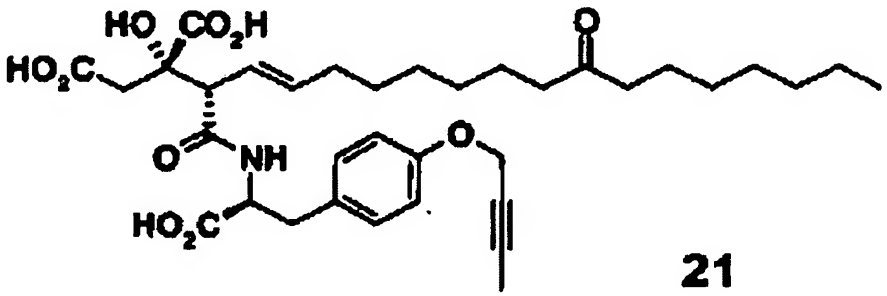
DETAILED ACTION

Species Election

Applicant's election with traverse of the specific and exact pharmaceutical composition/compound in the reply filed on 30 December 2008 is acknowledged. The traversal is on the ground(s) that the search of the elected sequence is not burdensome. This is not found persuasive because the current invention discloses variable representations of the core chemical moiety which would be burdensome to search in view of adequately determining patentability of the claimed invention.

For the reasons set forth in the Election/Restriction of 2 December 2008, the requirement for species election is maintained.

The requirement is still deemed proper and is therefore made FINAL.



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Compound 21 is a compound of the formula (I) in which X is 2- buthyn -1-yl and R3 is OH.

The traverse is not found persuasive, because it would be a burden to search each and every compound as disclosed in light of the elected compound.

Claims 10, 11, 19, and 20 read on the elected species, however the species election is not being maintained.

The elected species is not fairly taught in the prior art. Therefore, the search has been expanded to other and/or general species encompassed by the claims.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 2, 3, 4, 5, 6, 7, 8,9, 10, 11, 12, 15, 17, 18, 19, 20, and 21 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The term *prodrug* in the instant claims is not described, explained, or defined in the instant specification. The variability of the class of prodrugs for the compound as claimed is expansive in the art. However, the specification is silent with regard to any adequate disclosure with regard to subject matter clearly pointing out the distinction between a prodrug species as claimed and the pharmaceutical composition from which the alleged prodrug is based. It is art-known that prodrugs exemplify enhance properties in view of the parent drug. However, the specification only cites the term prodrug numerous times without an explanation based upon the limitation drawn to such in the instant claims.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 2, 3, 4, 5, 6, 7, 8,9, 10, 11, 12, 15, 17, 18, 19, 20, and 21 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the pharmaceutical composition, does not reasonably provide enablement for the prodrug of the said pharmaceutical composition. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized in Exparte Forman, 230 USPQ 546 (BPAI 1986) and reiterated by the Court of Appeals in In re Wands, 8 USPQ2d 1400 at 1404 (CAFC 1988). The factors to be considered in determining whether undue experimentation is required include:

1) the quantity of experimentation necessary

2) the amount of direction or guidance provided

3) the presence or absence of working examples

4) the nature of the invention

5) the state of the art

6) the relative skill of those in the art

7) the predictability of the art and

8) the breadth of the claims

The quantity of experimentation in order to determine if the prodrug of the pharmaceutical composition is enabled is absent in the whole specification. Palaska et al. (Synthesis and antidepressant activities of some 3,5 –diphenyl-2-pyrazolines, European Journal of Medicinal Chemistry, vol. 36, Issue 6, June 2001, pages 539-543) teach that

Prodrug-based monoamine oxidase (MAO) inhibitors have hydrazide, hydrazine and amine moiety such as isocarboxazid [6], phenelzine [7] and moclobemide [8 and 9] show prominent antidepressant activity in laboratory animals and man. Additionally, tranylcypromine-like MAO inhibitors are mechanism-based inactivators and they are metabolised by MAO with one electron of the nitrogen pair and to generate an imine, the other residing on a methylene carbon (R---C=NH_2^+). The structures of 3-aryl-2-pyrazoline derivatives are very similar to those of isocarboxazid (*figure 1*) and these compounds metabolise easily and show their activity as prodrug (Please see lines 8-17 of Introduction).

Thus, it is well-known in the art that due experimentation in order to clearly assess and determine the efficacy and safety of a prodrug is necessary. The reference also suggest that based upon the title compound as disclosed, the distinction was made with regard to the drug and any further activity exemplified as a prodrug.

Based upon the reference *supra*, it is not clear and highly unpredictable that the claims of the current invention drawn to prodrugs is enabled based upon the absence of evidence.

Further, direction and guidance in the specification is silent as to reasoning or disclosure about the prodrug limitation as cited in the majority of the claims cited.

The state of the art and nature of the invention are drawn to pharmaceutical compositions that require this particular distinction because of the relative toxicity of the pharmaceutical agents disclosed

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-14 and 21-24 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treating, does not reasonably provide enablement for preventing viral infectious diseases. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized in Exparte Forman, 230 USPQ 546 (BPAI 1986) and

reiterated by the Court of Appeals in In re Wands, 8 USPQ2d 1400 at 1404 (CAFC 1988). The factors to be considered in determining whether undue experimentation is required include:

1) the quantity of experimentation necessary

2) the amount of direction or guidance provided

3) the presence or absence of working examples

4) the nature of the invention

5) the state of the art

6) the relative skill of those in the art

7) the predictability of the art and

8) the breadth of the claims

The breadth of the claims, state of the art, and nature of the invention

The Epidemiology Program Office (EPO, hereinafter), Centers for Disease Control and Prevention (CDC) U.S. Department of Health and Human Services, Atlanta, GA. 30333, United States Department of Health and Human Services (Recommendations for Prevention and Control of Hepatitis C Virus (HCV) Infection and HCV-related Chronic Disease, October 16, 1998/Vol. 47/ No. RR-19, printed pages 1-40 disclose:

These recommendations are an expansion of previous recommendations for the prevention of hepatitis C virus (HCV) infection that focused on screening and follow-up

of blood, plasma, organ, tissue, and semen donors (CDC. Public Health Service inter-agency guidelines for screening donors of blood, plasma, organs, tissues, and semen for evidence of hepatitis B and hepatitis C. MMWR 1991; 40[No. RR-4]; 1-17). The recommendations in this report provide broader guidelines for a) preventing transmission of HCV; b) identifying, counseling, and testing persons at risk for HCV infection; and c) providing appropriate medical evaluation and management of HCV infected persons. Based on currently available knowledge, these recommendations were developed by CDC staff members after consultation with experts who met in Atlanta during July 15–17, 1998. This report is intended to serve as a resource for health-care professionals, public health officials, and organizations involved in the development, delivery, and evaluation of prevention and clinical services (Summary, penultimate paragraph).

The breadth of the claims is directed essentially to a single pharmaceutical compound/ composition for preventing or treating viral infectious diseases such as HCV. The breadth of the claims is directed specifically to prevention as a limitation. However, based on the disclosure of the reference *supra,* the breadth of the claims seem narrower than the breadth of the content of the EPO reference which essentially teach variable factors in the way of proper control of HCV.

The state of the art teaches:

Hepatitis C virus (HCV) infection is the most common chronic blood borne infection in the United States. CDC staff estimate that during the 1980s, an average of 230,000 new infections occurred each year (CDC, unpublished data). Although since 1989 the annual number of new infections has declined by >80% to 36,000 by 1996 (1, 2), data from the Third National Health and Nutrition Examination Survey (NHANES III), conducted

during 1988–1994, have indicated that an estimated 3.9 million (1.8%) Americans have been infected with HCV (3). Most of these persons are chronically infected and might not be aware of their infection because they are not clinically ill. Infected persons serve as a source of transmission to others and are at risk for chronic liver disease or other HCV-related chronic diseases during the first two or more decades following initial infection (page 9, 1st paragraph under Introduction).

The nature of the invention as disclosed *supra* in the breadth of the claims is drawn specifically and exclusively to the administration of an active agent in order to treat and ultimately prevent HCV.

However, the EPO reference adequately supports and suggests that there are many factors to the prevention of this blood-borne disease.

Reducing the burden of HCV infection and HCV-related disease in the United States requires implementation of primary prevention activities that reduce risks for contracting HCV infection and secondary prevention activities that reduce risks for liver and other chronic diseases in HCV-infected persons. In addition, surveillance and evaluation activities are required to determine the effectiveness of prevention programs in reducing incidence of disease, identifying persons infected with HCV, providing appropriate medical follow-up, and promoting healthy lifestyles and behaviors. Primary prevention activities can reduce or eliminate potential risk for HCV transmission from a) blood, blood components, and plasma derivatives; b) such high-risk activities as injecting-drug use and sex with multiple partners; and c) percutaneous exposures to blood in health care and other (i.e., tattooing and body piercing) settings.

Immunization against HCV is not available; therefore, identifying persons at risk but not infected with HCV provides opportunity for counseling on how to reduce their risk for becoming infected.

Elements of a comprehensive strategy to prevent and control hepatitis C virus (HCV) infection and HCV-related disease

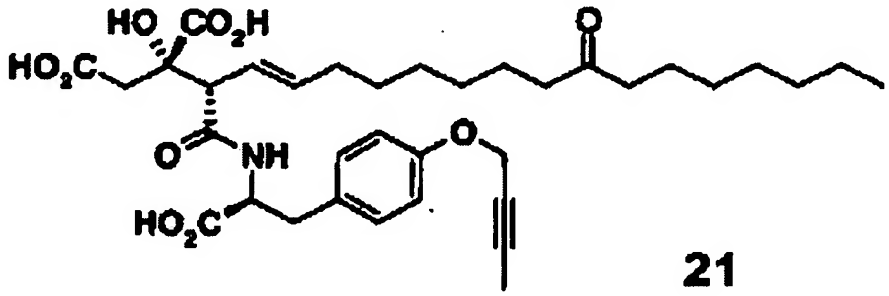
- Primary prevention activities include
  - screening and testing of blood, plasma, organ, tissue, and semen donors
  - virus inactivation of plasma-derived products;
  - risk-reduction counseling and services; and
  - implementation and maintenance of infection-control practices.
- Secondary prevention activities include
  - identification, counseling, and testing of persons at risk, and
  - medical management of infected persons.
- Professional and public education.
- Surveillance and research to monitor disease trends and the effectiveness of prevention activities and to develop improved prevention methods.

16 MMWR October 16, 1998

As disclosed above, medical management is a secondary preventative measure.

The amount of direction or guidance provided, the presence of absence of working examples

The specification does not provide cumulative results or correlative data in the way of clearly delineating prevention of HCV with compound 21 in Example 14 of the specification.



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Accordingly, it would be unclear to the one of ordinary skill as to how prevention is being determined with the administration of this compound wherein X is buthyn -1-yl and R3 is an OH.

Direction and guidance based on how to make these chemical moiety derivatives is replete and clearly represented throughout the whole specification. However, the specification is not commensurate in scope with the instant claims based on the absence and silence as to how the one of skill would use the structure represented above in the administration for the prevention of HCV.

The quantity of experimentation, the predictability of the art, and the relative skill of those in the art.

The EPO reference cites:

To prevent chronic HCV infection and its sequelae, prevention of new HCV infections should be the primary objective of public health activities. Achieving this objective will require the integration of HCV prevention and surveillance activities into

current public health infrastructure. In addition, several questions concerning the epidemiology of HCV infection remain, and the answers to those questions could change or modify primary prevention activities. These questions primarily concern the magnitude of the risk attributable to sexual transmission of HCV and to illegal noninjecting-drug use. Identification of the large numbers of persons in the United States with chronic HCV infection is resource-intensive. The most efficient means to achieve this identification is unknown, because the prevention effectiveness of various implementation strategies have not been evaluated. However, widespread programs to identify, counsel, and treat HCV-infected persons, combined with improvements in the efficacy of treatment, are expected to lower the morbidity and mortality from HCV-related chronic liver disease substantially. Monitoring the progress of these activities to determine their effectiveness in achieving a reduction in HCV-related chronic disease is important (please see FUTURE DIRECTIONS, page 33, penultimate paragraph).

The content of the specification discloses no quantity of experimentation in order to adequately assess prevention of HCV. Further, the extent of experimentation needed in order to adequately assess prevention would be undue and extensive based upon the teachings and protocols of the CDC and their recommendations and reports directed to control of HCV.

Likewise, based upon the disclosure *supra* entitled FUTURE DIRECTIONS, the specification makes no distinction with regard to a specific patient population by which HCV may be prevented.

Further, the claims of the invention fail to establish predictability in the way of prevention that this same invention is enabled with this actual chemical moiety for HCV. The

guidelines disclosed by the EPO reference clearly point out the variable factors that are implemented in order to affect any preventative objective.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Please be clear as to what are you examining in this art rejection. Is it the elected species? the full scope, or some thing in between?

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.

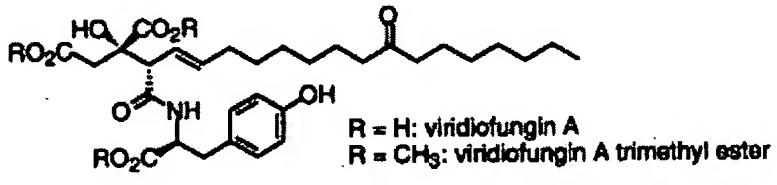
3. Resolving the level of ordinary skill in the pertinent art.

4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 15 - 24 are rejected under 35 U.S.C. 103(a) as being unpatentable over **Esumi et al.**, Synthesis of viridiofungin A trimethyl ester and determination of the absolute structure of viridiofungin A, Tetrahedron Letters/ Vol. 39, Issue 8, 1998, pages 877-880, printed pages 1-3

Esumi et al. teach four diastereoisomeric trimethyl esters of viridiofungin A, a member of novel family of aminoacyl alkyl citrate compounds, were synthesized in a highly stereoselective manner and the absolute configuration of natural viridiofungin A was determined to be 3*S*,4*S*,2'*S*.

Viridiofungin A trimethylester and its three diastereoisomers were synthesized, thereby establishing the absolute structure of natural viridiofungin A as depicted left (Abstract only).



Esumi et al. does not teach the viridiofungin A for the treatment of viral infections.

However, Esumi et al. teach a core chemical moiety which makes formula (I) of claim 15 and 21 obvious in view of the claimed invention.

1. Determining the scope and contents of the prior art.

2. Ascertaining the differences between the prior art and the claims at issue.

3. Resolving the level of ordinary skill in the pertinent art.

4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

The scope and content of the prior art adequately teaches the current invention via the chemical moieties of Esumi et al. The motivation to combine is further represented further by Esumi et al. because of the search extended to the other general species of the claimed invention. The claims are drawn to a pharmaceutical composition and the chemical moieties of Esumi et al. reasonably encompass the chemical moiety of the claimed invention.

The differences between the prior art and the claims at issue is that the chemical moiety as elected is taught *inter alia* (among other similarly related agents which share the same core moiety). Esumi et al. form a combination of references which, alone, fully make the compounds of formula (I) in claim 1 fully obvious in view of the claims of the invention.

Objective evidence drawn to obviousness are also disclosed in Esumi et al. which clearly teach the species of claims 15 and 21. Thus, it would be readily apparent to the one of skill to optimize characterization of such compounds in view of the elected species.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Timothy E. Betton whose telephone number is (571) 272-9922. The examiner can normally be reached on Monday-Friday 8:30a - 5:00p. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreeni

Padmanabhan can be reached on (571) 272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

TEB

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Supervisory Patent Examiner
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